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Spatiotemporal Brain Dynamics of Emotional Face Processing Modulations Induced by the Serotonin 1A/2A Receptor Agonist Psilocybin

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Emotional face processing is critically modulated by the serotonergic system. For instance, emotional face processing is impaired by acute psilocybin administration, a serotonin (5-HT) 1A and 2A receptor agonist. However, the spatiotemporal brain mechanisms underlying these modulations are poorly understood. Here, we investigated the spatiotemporal brain dynamics underlying psilocybin-induced modulations during emotional face processing. Electrical neuroimaging analyses were applied to visual evoked potentials in response to emotional faces, following psilocybin and placebo administration. Our results indicate a first time period of strength (i.e., Global Field Power) modulation over the 168–189 ms poststimulus interval, induced by psilocybin. A second time period of strength modulation was identified over the 211–242 ms poststimulus interval. Source estimations over these 2 time periods further revealed decreased activity in response to both neutral and fearful faces within limbic areas, including amygdala and parahippocampal gyrus, and the right temporal cortex over the 168–189 ms interval, and reduced activity in response to happy faces within limbic and right temporo-occipital brain areas over the 211–242 ms interval. Our results indicate a selective and temporally dissociable effect of psilocybin on the neuronal correlates of emotional face processing, consistent with a modulation of the top-down control.

Keywords: 5-HT1A/2A receptors, EEG, emotional face processing, psilocybin, source estimation

Introduction

Facial expressions provide information on our emotional state. Therefore, accurate face processing is essential for appropriate social interaction and behavior (Ekman et al. 1987). Furthermore, impaired emotional face processing has been closely related to mood disorders (e.g., major depression and anxiety). For instance, mood disorders patients, compared with healthy, are characterized by an increased attentional bias to negative stimuli (Disner et al. 2011) and enhanced neural response to threat stimuli within the extensive neural network of emotional face processing (Stuhmann et al. 2011).

Several studies demonstrated that serotonergic antidepressants shift the attentional bias from negative to positive, and reduce the neurophysiological response to threat stimuli (Harmer 2008 for discussion), providing evidence for a critical role of the serotonergic system in emotional face processing.

Selective serotonin reuptake inhibitors (SSRIs) administration causes an overall increase of extracellular serotonin (5-HT) level in the brain (Savitz et al. 2009), by reducing pre-synaptic serotonin reuptake (Nutt et al. 1999). Behaviorally, acute SSRIs administration in healthy subjects improve the recognition of both fearful (Browning et al. 2007) and happy

faces (Harmer et al. 2002), whereas prolonged administration reduces the recognition of fearful faces (Harmer et al. 2004).

Furthermore, neuroimaging studies revealed a face valence selective effect of SSRIs on neural processing. For instance, causing a reduced neural response to fearful faces within the amygdala, parahippocampal, and medial prefrontal cortex (Del-Ben et al. 2005; Harmer et al. 2006; Anderson et al. 2007; Norbury et al. 2007; Murphy et al. 2009). Results for happy faces processing are less consistent, showing either an increased (e.g., Norbury et al. 2007) or nonsignificantly decreased (e.g., Murphy et al. 2009) amygdala activity after SSRIs administration.

Growing evidence suggests that specific serotonin receptor subtypes are critically involved in mood disorders (Millan 2006; Sharp and Cowen 2011). For instance, it has been shown that the selective 5-HT1A/2A receptor agonist psilocybin modulates the neural activity within circuits related to emotion regulation (Nichols 2004; Vollenweider and Kometer 2010; Carhart-Harris, Erritzoe, et al. 2012; Carhart-Harris, Leech, et al. 2012). Accordingly, acute psilocybin administration modulates emotional face processing (Kometer et al. 2012; Schmidt et al. 2013). For instance, Schmidt et al. (2013) demonstrated that psilocybin reduces the electrophysiological response to both neutral and fearful faces. Specifically, they showed a temporal selective effect of psilocybin on emotional face processing; psilocybin did not modulate the first rapid-course emotion categorization, occurring at ~100 ms poststimulus onset, but rather the fine-grained analysis of the facial features (i.e., “structural encoding”), occurring at ~170 ms.

Taken together, these results provide a first evidence that the selective 5-HT1A/2A receptor agonist psilocybin modulates emotional face processing. However, the spatiotemporal dynamics of the neurophysiological alterations underlying these psilocybin-induced effects remains poorly understood.

To further elucidate this issue, in the present study we conducted electrical neuroimaging analyses on visual evoked potentials (VEPs) in response to facial expressions (fearful, happy, and neutral) under placebo and psilocybin. Electrical neuroimaging analyses allow to differentiate modulations in response strength and topography, and localize effects using a distributed source model (LAURA) (Michel et al. 2004; Murray et al. 2008). Thus, the present study provides a differentiated description of the neurophysiological mechanisms underpinning psilocybin's effects on emotional face processing.

Materials and Methods

Participants

Thirty healthy (27 right-handed) participants 16 males (mean ± SEM age: 25 ± 0.6 years), with normal or corrected-to-normal vision

participated in the study. Participants were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. They were screened by the DIA-X diagnostic expert system (Wittchen and Pfister 1997), a semistructured psychiatric interview to exclude individuals with personal or family (first-degree relatives) histories of major psychiatric disorders, and by the Symptom Checklist (SCL-90-R) (Derogatis 1994). Furthermore, they underwent to the Mini-International Neuropsychiatric Interview (M.I.N.I.), a structured psychiatric interview (Sheehan et al. 1998). Participants were excluded, if they had history of drug dependence, as assessed by a self-made consumption questionnaire, or if they were currently using drugs as assessed by a urine drug test. Nevertheless, seven participants were occasional smokers (<6 cigarettes/day), 7 participants reported a sporadic or rare cannabis use in the past (<2 joints/month), one participant reported previous experience with MDMA (one pill lifetime), and one reported previous experience with psilocybin (one administration lifetime).

The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion. The use of psilocybin was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Berne, Switzerland.

Drug Administration

Using a randomized, double-blind, placebo-controlled design, all participants received either psilocybin or placebo in 2 separate sessions, separated by at least 2 weeks.

Psilocybin was obtained through the Swiss Federal Office for Public Health. Psilocybin (170 µg/kg) and lactose placebo were administered in gelatin capsules of identical number and appearance, as previously described (Kometer et al. 2011; Schmidt et al. 2013). Participants remained monitored until all acute drug effects had worn off, and were subsequently released into the custody of a partner.

Psychological Assessment

The Altered State of Consciousness (ASC) questionnaire, a visual analog and self-rating scale, was used to assess the subjective psychological effects induced by psilocybin (Dittrich 1998). A recent evaluation of the ASC questionnaire has constructed eleven new lower order scales (Studerus et al. 2010), which were used in this study. The ASC questionnaire was applied 360-min post-treatment to retrospectively rate subjective experiences since drug intake.

Stimuli and Task Design

The experiment consisted in an EEG passive-viewing emotional face task. All target emotional faces were backward masked with a neutral face. Participants were instructed to determine the emotional valence of each face (neutral, fearful, and happy) no response was required. They performed the experiment twice (distinct sessions/days), one for each treatment (i.e., placebo and psilocybin).

Stimuli were black and white images taken from the Ekman–Friesen series (Ekman and Friesen 1976). The target images were neutral and basic emotional expressions (i.e., fearful and happy faces). The masking photograph was always a neutral face of the same identity. For each face valence, 6 different identities were used. To limit confounds by low-level face processing qualities, faces were modified using Photoshop 2.0 (Adobe Systems Incorporated, San Jose, CA, USA) such that task-irrelevant features were removed and that the only visible features of the faces were the eyes, eyebrows, nose, and mouth. Stimuli were displayed in the center of the monitor and subtended a visual angle of 3° horizontally and 4.4° vertically.

Each trial began with a fixation cross lasting for 2000 ms. The target faces (i.e., neutral, fearful, and happy) were presented for either 10 ms (unconscious condition) or 200 ms (conscious condition) (Williams et al. 2004). Each target face was immediately followed by a mask (i.e., neutral face) lasting for 150 ms. For each experimental session, a total of 40 trials (target-mask pairs) were presented for each face valence and for the 2 target durations, resulting in a total of 240 images. Target

faces were randomly presented with equal probability. The experiment was conducted in a sound attenuated and electrically shielded booth. Stimulus delivery and participants' responses were controlled by Eprime 2.0 (Psychology Software Tools, PA, USA). Timing issues were controlled using an oscilloscope. Because recent evidence revealed that psilocybin attenuates the explicit recognition of negative expressions (Kometer et al. 2012) and that its effect on VEPs to emotional face expressions were more pronounced during conscious than nonconscious processing (Schmidt et al. 2013), in the present study, we specifically aimed to further explore the effect of psilocybin on the conscious processing of emotional faces by disentangling the spatiotemporal brain dynamics of this effect. The EEG data recorded during unconscious face processing will be included in a further study.

EEG Acquisition and Preprocessing

Continuous EEG was acquired at 512 Hz through a 64-channel Biosemi ActiveTwo AD-box referenced to the common mode sense (CMS; active electrode) and grounded to the driven right leg (DRL; passive electrode), which functions as a feedback loop driving the average potential across the electrode montage to the amplifier zero. Data preprocessing and analyses were performed using Cartool Software (Brunet et al. 2011; <http://sites.google.com/site/fbmlab/cartool>). The EEG epochs were defined from 100 ms prestimulus (i.e., emotional face) to 500 ms poststimulus onset. All analyses were always conducted over the full ERP epoch. EEG epochs from 100 ms pre- to 500 ms post-stimulus onset were averaged from each participant to calculate ERPs for each treatment (i.e., placebo or psilocybin) and face valence (i.e., neutral, fearful, and happy), generating separate 2 × 3 within-subject designs. In addition to visual inspection, a semiautomated ±60 µV artifact rejection criterion was applied in order to reject epochs with eye blinks and/or other sources of transient noise. Prior to group-averaging for each experimental condition, data at artifact-contaminated electrodes from each participant were interpolated using 3D splines (Perrin et al. 1987). Data were then recalculated against the average reference and band-pass-filtered (0.18–40 Hz). The baseline was defined as the 100 ms prestimulus period. No prestimulus baseline correction was applied for the following reasons: 1) we could not assume that the preparatory processes were similar across conditions (i.e., with and without treatment) 2) baseline correction can affect the topography of the data and potentially shift statistical effects in time (Michel et al. 2009; Tzovara et al. 2012 for discussion).

The average number of accepted EEG epochs per each drug condition were: Condition 1 (placebo) neutral face: (mean ± SEM; 32.8 ± 1.13), fearful face: (mean ± SEM; 32.5 ± 1.35), happy face (mean ± SEM; 31.86 ± 1.23); condition 2 (psilocybin) neutral face: (mean ± SEM; 31.5 ± 1.26), fearful face: (mean ± SEM; 31.13 ± 1.26), happy face (mean ± SEM; 30.09 ± 1.19). Conditions were not significantly different (2-way ANOVA: interaction treatment × face: $F_{2,58} = 0.177$; P -values > 0.8; main effect face: $F_{2,58} = 1.41$; P -values > 0.3; main effect treatment: $F_{1,29} = 0.64$, P -values > 0.5). Because the number of accepted epochs did not differ significantly across conditions we can exclude that our effects followed from differences in signal-to-noise ratios.

EEG Analyses and Source Estimation

General Analysis Strategy

Effects of psilocybin on emotional face processing were identified with a stepwise analysis procedure referred as electrical neuroimaging, implemented in Cartool (Brunet et al. 2011; <http://sites.google.com/site/fbmlab/cartool>). By analyzing the ERPs using Electrical Neuroimaging, we were allowed to assess and differentiate effects following from: 1) strength modulations of statistically indistinguishable generator configurations (i.e., Global Field Power modulations in absence of topographic modulations), 2) topographic modulations across conditions, resulting from changes in the intracranial sources configuration, 3) latency shifts across conditions. Because each analyses is independent one from the other, any combination of these neurophysiologic phenomena can be assessed (Michel et al. 2004, 2009; Murray et al. 2008). Finally, we used the local autoregressive average

distributed linear inverse solution (LAURA; Grave de Peralta Menendez et al. 2001, 2004) to visualize and statistically assess the likely underlying sources of effects identified in the previous analysis steps (GFP and/or topographic modulations).

Voltage Waveform Analyses

A first level of analysis was performed by submitting the VEPs data to a 2-way ANOVA using the within-subject factors treatment (placebo; psilocybin) and face valence (neutral; fear; happy) at each scalp electrode as a function of peristimulus time. Note that only effects meeting or exceeding the P -values 0.05 criterion for at ~15 consecutive milliseconds were considered reliable (Guthrie and Buchwald 1991). This analysis was included to give a visual impression of specific effects within the dataset, and to facilitate the contextualization of our results with other VEP studies (e.g., Schmidt et al. 2013). However, due to the electrode reference-dependent nature of statistical analyses of AEP waveforms (a change of the reference electrode will result in a change in statistical outcomes (Tzovara et al. 2012 for discussion), our primary analyses and basis for interpretation were the electrode reference-independent analyses detailed below.

Global Electric Field Analyses

Changes in the strength of the electric field at the scalp were calculated using the global field power (GFP), a reference electrode-independent analyses (Murray et al. 2008; Koenig and Melie-García 2010), for each participant and experimental condition. GFP measures the strength of the electric field at the scalp, independently of its spatial distribution across the electrode montage (Lehmann and Skrandies 1980; Murray et al. 2008, 2009). The GFP is calculated as the square root of the mean of the squared value recorded at each electrode and represents the spatial standard deviation of the electric field at the scalp at each instant in time. Modulations in GFP were statistically analyzed at each time-point using a 2-way ANOVA using within-subject factors of treatment and face valence. We would like to point out that to reduce the risk of false-positive results arising from multiple tests only effects at least of a P -values 0.05 criterion lasting at least ~15 consecutive milliseconds were considered reliable (Guthrie and Buchwald 1991, similar criteria were used previously, e.g., De Lucia et al. 2010; Knebel et al. 2011; Cappe et al. 2012).

Topographic Modulations Analyses

Topographic modulations were identified using global dissimilarity (DISS) (Lehmann and Skrandies 1980), which is calculated as the root mean square of the difference between 2 strength-normalized vectors (i.e., the instantaneous voltage potentials across the electrode montage). The DISS value between the face valences as a function of treatment were compared time-point by time-point with an empirical distribution derived from a bootstrapping procedure (5000 permutations per data point), based on randomly reassigning data across conditions for each participants (detailed in Murray et al. 2008; Koenig et al. 2011). DISS is an electrode reference-independent analysis. Moreover, GFP and DISS are 2 orthogonal analyses because DISS is insensitive to pure amplitude modulations across conditions. A topographic modulation is neurophysiological interpreted as a changes following from a significant differences in the configuration of the intracranial generators (Lehmann 1987). As for GFP analyses, temporal autocorrelation was corrected through the application of a ~15 continuous milliseconds as temporal criterion for the persistence of differential significant effects (Guthrie and Buchwald 1991, similar criteria were used previously, e.g., De Lucia et al. 2010; Knebel et al. 2011; Cappe et al. 2012).

Source Estimations

We estimated the electrical activity in the brain using a distributed linear inverse solution applying the local autoregressive average regularization approach (LAURA), comprising biophysical laws as constraints (Grave de Peralta Menendez et al. 2001; 2004; Michel et al. 2004). For the lead field matrix calculation, we applied the spherical model with anatomical constraints (SMAC) method (Spinelli et al.

2000), which transforms the MRI to the best-fitting sphere using homogeneous transformation operators. It then determines a regular grid of 3005 solution points in the gray matter of this spherical MRI and computes the lead field matrix using the known analytical solution for a spherical head model with 3 shells of different conductivities as defined by Ary et al. (1981).

The periods of significant treatment \times face valence interaction determined in the GFP analysis were used as period of interest, on which carry out the source estimations for each experimental condition. To increase the signal-to-noise ratio, VEPs for each participant and each experimental condition were separately averaged across the above-mentioned time periods when significant treatment \times face valence interactions were identified in the GFP analysis. The inverse solution was then estimated for each of the 3005 nodes. These data were then submitted to a 2-way ANOVA using within-subject factors of treatment and face valence. To correct for multiple testing and temporal autocorrelation, only nodes with P -values <0.05 2-tailed and clusters of at least 21 contiguous nodes were considered significant (these criteria were published elsewhere, e.g., Bernasconi et al. 2011). The spatial criterion was determined using the AlphaSim program (<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>). The results of source estimations were rendered on the Montreal Neurological Institute's average brain with the Talairach and Tournoux (1988) coordinates.

Results

Psychometrics

Psilocybin produced alterations on the global ASC scores (Fig. 1). A 2-way treatment \times scale interaction indicated significant difference on specific scales ($F_{1,319} = 11.263$; $P < 0.001$). Furthermore, post hoc testing on this interaction showed that psilocybin versus placebo significantly increased all scores (all P -values <0.001 ; Bonferroni corrected), with the exception of anxiety (P -value >0.9 ; Bonferroni corrected) and spiritual experience scores (P -values >0.4 ; Bonferroni corrected).

VEP Waveform Analysis

A first level of analysis of the VEPs to emotional faces was performed using individual voltage waveforms, visual inspection of an occipital electrode (P8) indicate several effects: first a main effect of treatment, such that psilocybin appears to reduce the N170 response and a shift in latency, to the right, at ~200 ms poststimulus, independently of the face valence. Second, as expected, the N170 component is modulated by the emotional faces (fear and happy) vs. neutral face. These observations were statistically evaluated via a timewise 2-way ANOVA (treatment \times face valence). A significant (P -value <0.05 ; >15 continuous milliseconds) treatment \times face interaction was observed over the period 152–183 and 193–265 ms (Fig. 2a). Furthermore, there was a main effect of treatment (P -value <0.05 ; >15 continuous milliseconds) over the 152–183 and 193–265 ms poststimulus interval; a main effect of face (P -value <0.05 ; >15 continuous milliseconds) was observed over 66–92, 105–220, and 230–367 ms poststimulus interval (results not shown).

A second level of analysis of the VEPs was performed using group-averaged VEPs evoked by emotional face (i.e., neutral, happy and fear), which were compared as a function of treatment (placebo vs. psilocybin). Time-wise 2-way ANOVA (treatment \times face valence) analyses was performed as a function of peristimulus time at each of the scalp electrodes. Statistically significant interaction between treatment and face valence (P -value <0.05 , >15 consecutive milliseconds) were

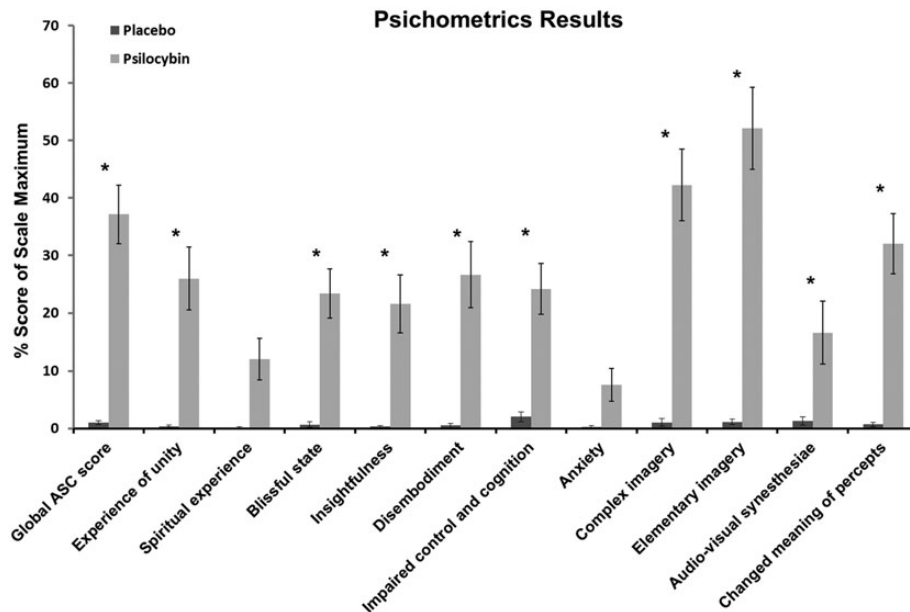


Figure 1. Psychometrics results. Effects of psilocybin on the ASC scales. Mean scores \pm SEM. Asterisks indicate significant differences between treatments. Symptoms scores were expressed as percent of scale maximum.

observed at ~100–300 ms poststimulus stimulus (Fig. 2*b*). Furthermore, a main effect of treatment was observed over the period: ~120–140, ~170–220 and ~230–400 ms poststimulus and a main effect of face valence over the period: ~160–200 and ~240–360 ms (Figs. 3*a* and 4*a*).

The reader should have in mind that our conclusions over the possible causes of the psilocybin-induced modulation of emotional face processing are based on analyses of electrode reference-independent features of the global electric field at the scalp (see below).

Global Electric Field Analyses

Of main interest to the aims of the present study, the time-point by time-point 2-way ANOVA on GFP evidenced a significant interaction between treatment and face valence over the period 168–189 ms ($F_{2,51} = 8.673$; $P = 0.00051$) and 211–242 ms ($F_{2,51} = 7.365$; $P = 0.0014$) after the stimulus onset (Fig. 2*c*), in accordance with a psilocybin-induced response modulation (vs. placebo).

Post hoc *t*-test on GFP over the 168–189 ms pointed out a significant decrease in GFP for both neutral and happy (P -values < 0.01 ; Bonferroni corrected), while over the period 211–242 ms a significant decrease in GFP only for happy faces (P -value < 0.01 ; Bonferroni corrected) (results not shown).

A main effect of treatment (t -values > 3.565 ; P -values < 0.05 ; > 15 consecutive milliseconds) was observed over the 94–143 and 180–219 ms poststimulus periods, and a main effect of face valence (t -values > 2.536 ; P -values < 0.05 ; > 15 consecutive milliseconds) over the 37–59, 105–139, 176–246 and 303–354 ms poststimulus periods (Figs. 3*b* and 4*b*).

By contrast, the nonparametric DISS statistics (used to assess topographic modulations across conditions) did not reveal significant interaction between treatment and face valence over the 500 ms poststimulus (P -values < 0.05 ; > 15 consecutive milliseconds; Figure 2*d*). A main effect of treatment was observed over the –26–103; 99–219; 110–220 and 230–304 ms poststimulus periods (Fig. 3*c*) and a main effect of face

valence over the 156–214 and 250–364 ms poststimulus periods (Fig. 4*c*).

Since the aim of the study was to identify neurophysiological modulation induced by psilocybin to emotional face processing, the 2 periods of significant GFP interaction (treatment \times face valence) were selected as time period submitted to source estimations.

Source Estimations

LAURA distributed source estimations were calculated over the 168–189 and 211–242 ms poststimulus time periods, which indicated a significant GFP interaction between treatment and face valence.

Over the 168–189 ms period a significant interaction treatment \times face valence ($F_{2,58} > 5.26$; P -values < 0.03 ; $kE = 21$ contiguous solution points) was observed within the visual areas (right fusiform gyrus), limbic areas (bilateral parahippocampal gyrus, middle-posterior cingulate cortex and amygdala), temporoparietal areas (right insula; left middle-superior temporal gyrus) and the prefrontal areas (right inferior frontal cortex) (Fig. 5*a*). Over the 211–242 ms period a significant interaction ($F_{2,58} > 10.13$; P -values < 0.01 ; $kE = 21$ contiguous solution points) was observed within the visual area (right lingual gyrus, fusiform gyrus and middle-inferior occipital gyrus), the limbic areas (bilateral hippocampus and right parahippocampal gyrus), temporoparietal areas (middle-inferior temporal gyrus) and the prefrontal areas (right precentral gyrus) (Fig. 5*c*).

To assess the basis of the significant treatment \times face valence, brain regions indicating significant treatment \times face interaction (see above) were subdivided in distinct clusters according to literature (e.g., Fusar-Polli et al. 2009), and the group-average scalar values across the nodes within each clusters were calculated (shown as bar graphs in Fig. 5*b* and *d*). Over the first time period of interest (168–189 ms) in all 4 clusters (i.e., left STG; bilateral cingulate cortex; left parahippocampal gyrus and right insula/parahippocampal gyrus) significant

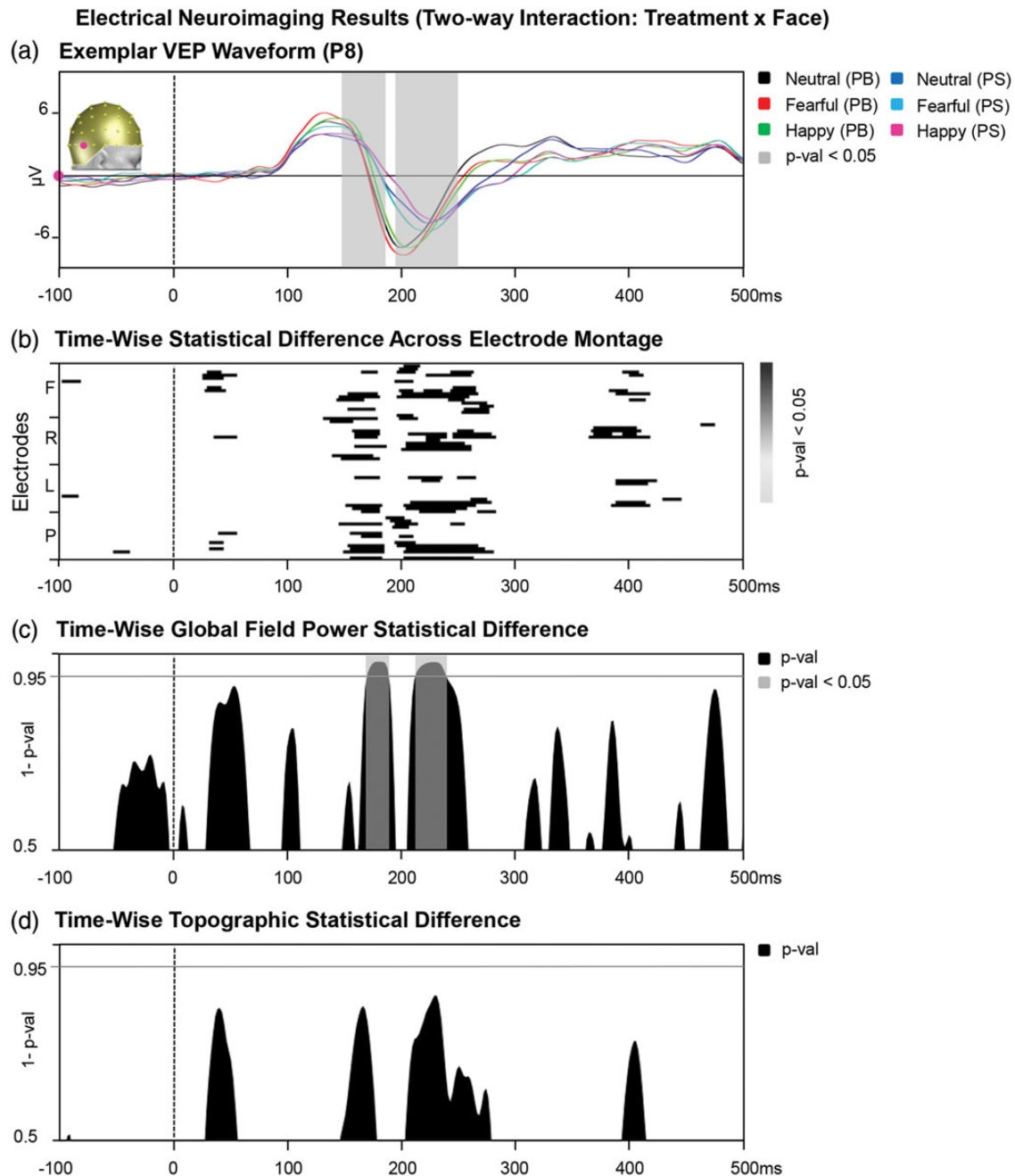


Figure 2. (a) Electrical neuroimaging results. Exemplar VEP waveform from a right occipital electrode (P8). VEP in response to neutral (black trace), fearful (red trace), happy face (green trace) under placebo. VEP in response to neutral (dark blue), fearful (light blue trace), happy face (pink trace) under psilocybin. Traces are displayed in microvolts as a function of time relative to onset of the emotional face. The time period with a significant interaction treatment \times face is indicated with a gray square ($P < 0.05$ for at least ~ 15 consecutive milliseconds). (b) VEP voltage waveform analyses. The results of the millisecond-by-millisecond 2-way ANOVA (treatment \times face valence) at each of the scalp electrodes from the group-averaged VEP waveforms are shown (only $P < 0.05$ for at least ~ 15 consecutive milliseconds). (c) Results of the millisecond-by-millisecond 2-way ANOVA analysis (black line; interaction treatment \times face) of the global field power over the entire epoch. Period of significant ($P < 0.05$ for at least ~ 15 consecutive milliseconds) GFP interaction treatment \times face are marked in gray. (d) Results of the millisecond-by-millisecond 2-way ANOVA of the global dissimilarity. Period of significant ($P < 0.05$ for at least ~ 15 consecutive milliseconds) topographic interaction treatment \times face are marked in gray.

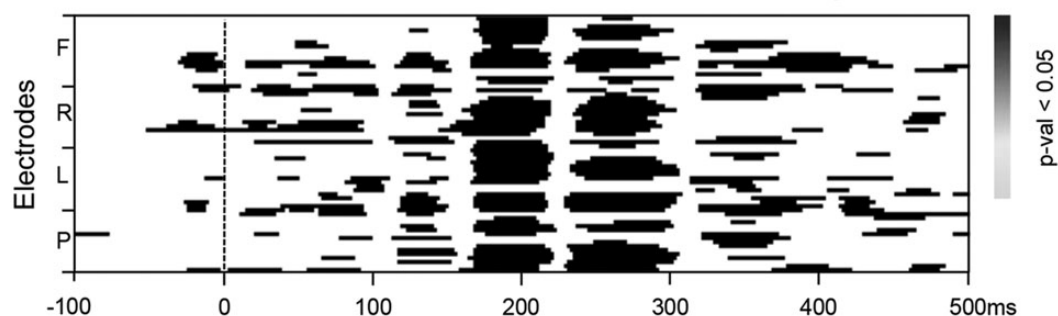
(P -values < 0.01 ; Bonferroni corrected) reductions of the activity were observed for both neutral and fearful faces, but not for happy faces (P -values > 0.5). Over the second period of interest (211–242 ms) for all clusters (i.e., right prefrontal cortex; right occipito-temporal cortex; left STG) significant (P -values < 0.01 ; Bonferroni corrected) reductions in the neurophysiological response were observed exclusively for the happy faces.

Discussion

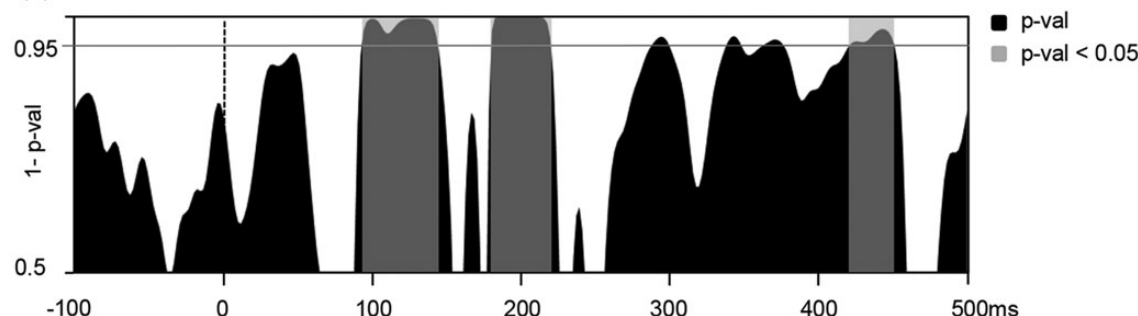
We identified the spatiotemporal brain dynamics underlying emotional face processing modulations induced by psilocybin, a serotonin 5-HT_{1A/2A} receptor agonist. Brain mechanisms associated with such modulations were identified by applying electrical neuroimaging analyses to the VEPs in response to emotional faces as a function of treatment (i.e., placebo vs.

Electrical Neuroimaging Results (Main effect of Treatment)

(a) Time-Wise Statistical Difference Across Electrode Montage



(b) Time-Wise Global Field Power Statistical Difference



(c) Time-Wise Topographic Statistical Difference

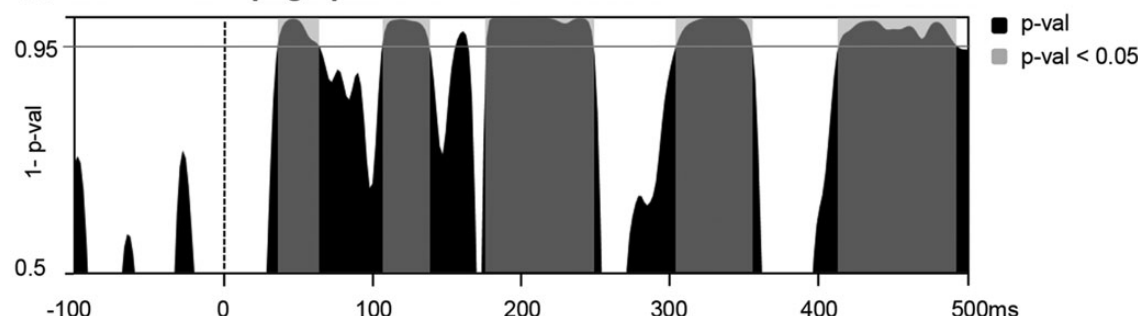


Figure 3. (a) Electrical neuroimaging results. VEP voltage waveform analyses. The results of the millisecond-by-millisecond main effect of treatment at each of the scalp electrodes from the group-averaged VEP waveforms are shown (only $P < 0.05$ for at least ~15 consecutive milliseconds). (b) Results of the millisecond-by-millisecond main effect of treatment (black line) of the global field power over the entire epoch. Period of significant ($P < 0.05$ for at least ~15 consecutive milliseconds) GFP interaction treatment \times face are marked in gray. (c) Results of the millisecond-by-millisecond main effect of treatment of the global dissimilarity. Period of significant ($P < 0.05$ for at least ~15 consecutive milliseconds) topographic interaction treatment \times face are marked in gray.

psilocybin). We identified 2 distinct time periods of strength (GFP) modulation induced by psilocybin administration. Distributed source estimations over these 2 time periods further indicated a face valence specific effect of psilocybin. The collective findings support a model in which serotonin 5-HT_{1A/2A} receptor stimulation has selective and temporal dissociable effects on the neuronal correlates of emotional face processing.

The latencies of our effects are consistent with a modulation of the fine-tuning categorization of facial expressions (Adolphs 2002). According to both animal intracranial recording and human electrophysiological studies, which investigated emotional face processing, an initial coarse categorization of the face occurs already at ~100 ms poststimulus, as suggested by an increased electrophysiological response to both face vs. object and emotional faces vs. neutral faces (Sugase et al. 1999;

Adolphs 2002). The initial categorization is succeeded by a fine-grained encoding (i.e., “structural encoding”) of facial features, as suggested by an increased electrophysiological response to emotional faces observed ~50 ms after the coarse categorization (Pegna et al. 2008; Smith 2012, Schmidt et al. 2013).

Furthermore, the latency of our effects are also consistent with previous studies, which investigated effects of serotonergic manipulation on faces processing. For instance, Schmidt et al. (2013) demonstrated a psilocybin-induced modulation of the structural encoding of emotional faces occurring at ~170 ms after the stimulus onset. However, further studies, which investigated the effects of acute selective serotonin reuptake inhibitors (SSRIs), observed a modulation of the emotional “expression decoding” (occurring at ~250 ms) but not of the

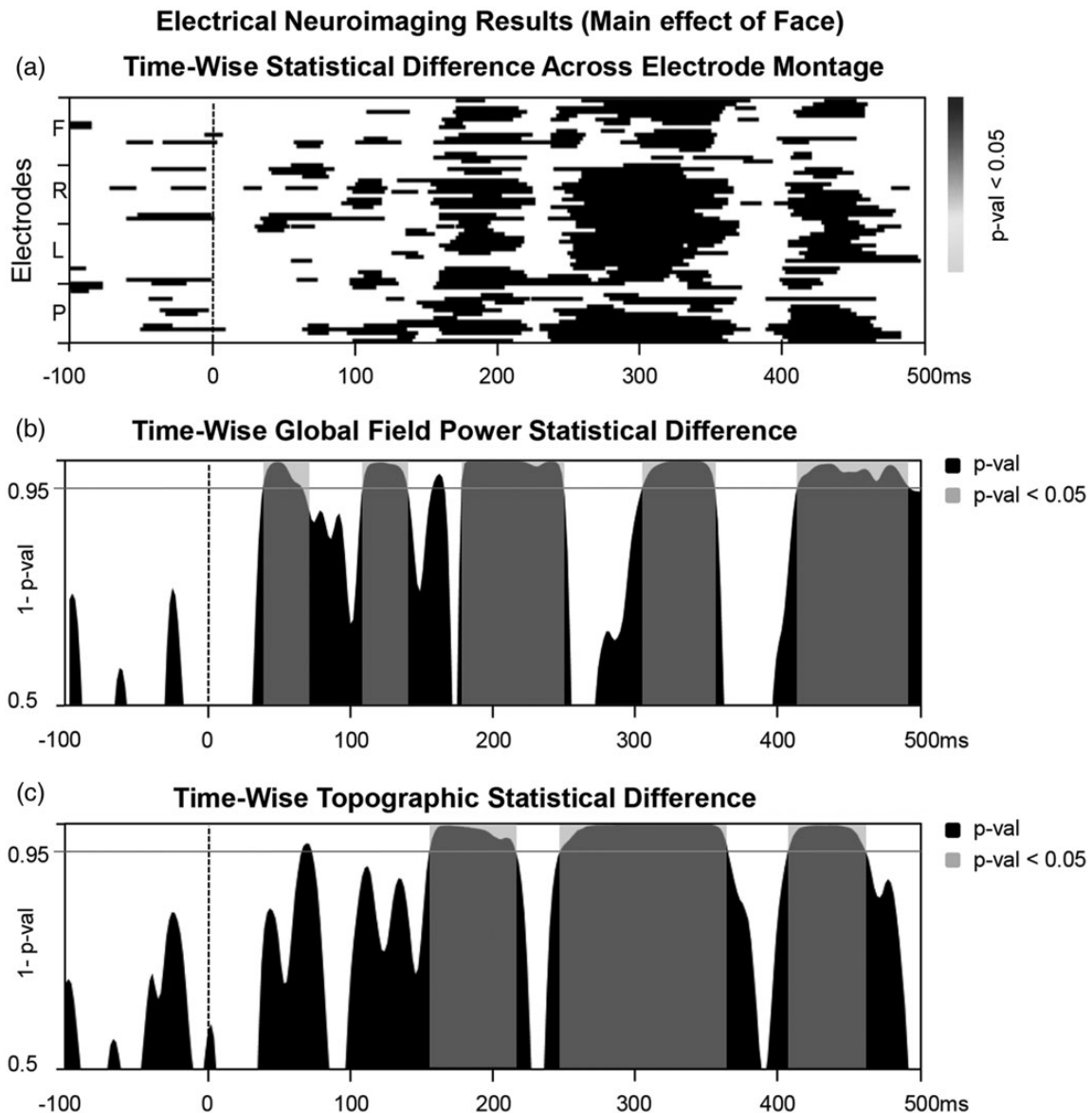


Figure 4. (a) Electrical neuroimaging results. VEP voltage waveform analyses. The results of the millisecond-by-millisecond main effect of face valence at each of the scalp electrodes from the group-averaged VEP waveforms are shown (only $P < 0.05$ for at least ~15 consecutive milliseconds). (b) Results of the millisecond-by-millisecond main effect of face (black line) of the global field power over the entire epoch. Period of significant ($P < 0.05$ for at least ~15 consecutive milliseconds) GFP interaction treatment \times face are marked in gray. (c) Results of the millisecond-by-millisecond main effect of face of the global dissimilarity. Period of significant ($P < 0.05$ for at least ~15 consecutive milliseconds) topographic interaction treatment \times face are marked in gray.

“structural encoding” (Kerestes et al. 2009; Labuschagne et al. 2010). The incongruence with our results might be due to a more specific effect of psilocybin vs. SSRIs on the 5-HT system (see Nichols 2004 and Elliott et al. 2011 for discussion).

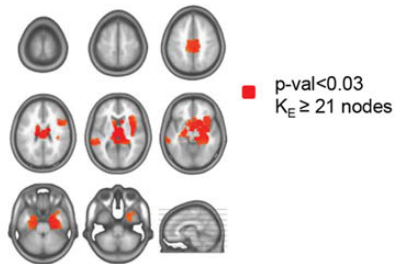
Source estimations over the 168–189 ms time period revealed a reduced neurophysiological response to both neutral and fearful faces within right fusiform gyrus, temporoparietal cortices, prefrontal areas and bilateral limbic areas, as well as a reduced response to happy faces within the right lingual gyrus, fusiform gyrus, middle-inferior occipital gyrus, bilateral limbic areas, temporoparietal cortices and the prefrontal areas over the 211–242 ms poststimulus period.

The temporal selective effects of psilocybin on emotional face processing (i.e., initial effect on both fearful and neutral faces, followed by effect on happy faces) are consistent with previous

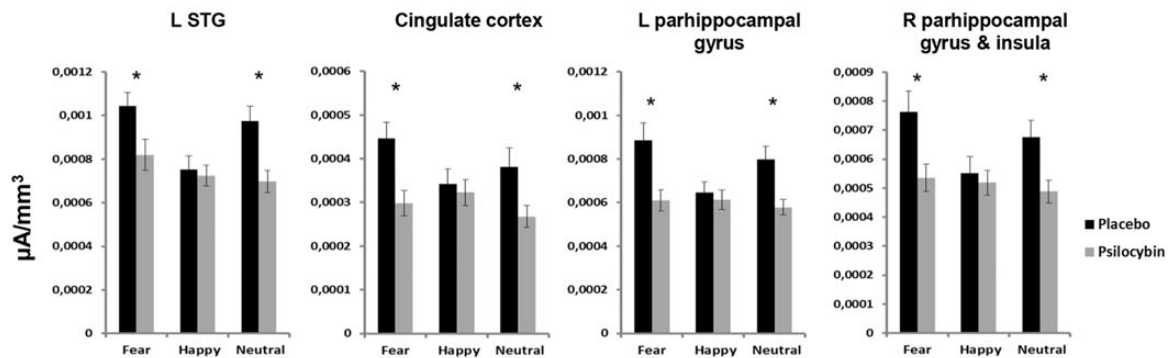
ERPs studies, which suggested a faster processing of negative compared with positive stimuli, due to the ecological importance of detecting signals of danger (Williams et al. 2006). However, few ERPs studies demonstrated that happy faces are processed faster than fearful faces (e.g., Batty and Taylor 2003). According to the authors, this counterintuitive result might be explained by the fact that negative stimuli are processed within a subcortical-slower pathway via the superior colliculus and pulvinar to the amygdala, consistent with anatomical studies in monkey (Day-Brown et al. 2010). Furthermore, over both periods of interest a stronger activity was localized predominantly within the right hemisphere, in line with previous studies that demonstrated a right lateralization of the emotional processing within the first 200 ms poststimulus (e.g., Williams et al. 2006; Fusar-Poli et al. 2009 for discussion).

Electrical Sources Analyses

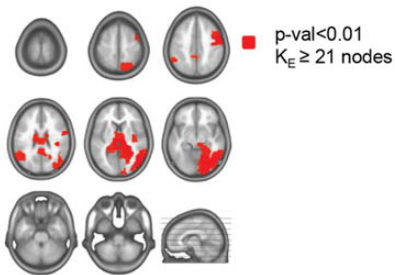
(a) LAURA Source Estimation Loci Exhibiting a Significant Treatment * Face Valence Interaction (168-189ms)



(b) Mean Scalar Value Within Each Cluster



(c) LAURA Source Estimation Loci Exhibiting a Significant Treatment * Face Valence Interaction (211-242ms)



(d) Mean Scalar Value Within Each Cluster

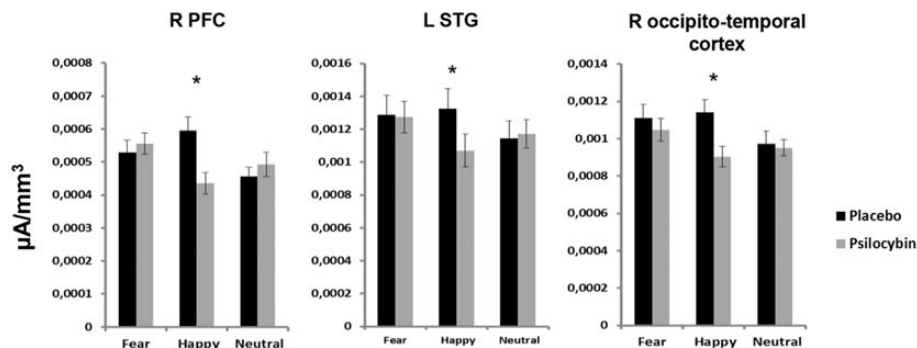


Figure 5. Statistical analyses of the source estimations 2-way interaction. Group-averaged source estimations were calculated over the periods 168–189 and 211–242 ms poststimulus for each experimental condition and submitted to a 2-way ANOVA. Regions exhibiting significant interaction treatment \times face are shown in panels *a* and *c* on axial slices of the MNI template brain. Only nodes meeting the P -values < 0.03 and the spatial criterion of at least 21 contiguous nodes were considered reliable *b* and *d*. indicate the mean scalar value of distinct clusters, asterisk indicate significant difference between placebo and psilocybin.

Furthermore, our source localizations are consistent with previous fMRI studies, which investigated neurophysiological modulations induced by citalopram, a SSRI (Anderson et al. 2007; Harmer 2008). For instance, neurophysiological modulations were observed within the “core system” of the emotional face processing network (Haxby et al. 2000), comprising occipital face-sensitive areas, the lateral fusiform gyrus (identity recognition), the superior temporal cortex (expression recognition), and within the “extended system” including the amygdala, the orbitofrontal cortex and the posterior cingulate cortex (emotion recognition) (Paulus et al. 2005; Anderson et al. 2007; Arce et al. 2008; Wingen et al. 2008; Bruhl et al. 2010).

During emotional face processing, these regions are functionally connected (e.g., Dima et al. 2011; Disner et al. 2011; Zhen et al. 2013), where the key structure of this network is the amygdala (e.g., Pessoa and Adolphs 2010). Thus, the observed impaired emotional face processing after psilocybin administration might be associated with an impaired functional connectivity between the amygdala and other key structures for emotional face processing (Vollenweider and Komater 2010 for discussion). However, this is clearly speculative. In fact, in the present study used source localization exclusively to identify changes in neural activity induced by psilocybin and did not taken into account changes in functional connectivity among regions critically involved during emotional faces processing. This issue will be addressed in further connectivity studies.

Furthermore, the difference between the effects induced by SSRIs (increased or no effect) and psilocybin on happy face processing might be due to different pharmacological effect of the 2 compounds. Whereas SSRIs increase serotonin level in the whole brain (Nutt et al. 1999; Murphy et al. 2009; Norbury et al. 2007; Elliott et al. 2011), psilocybin has a more specific affinity for serotonin 2A receptors, essentially located on the pyramidal cells within the PFC (Vollenweider et al. 1997; Nichols 2004). Accordingly, reduced serotonin level by acute tryptophan depletion (ATD) did not modulate the structural encoding of emotional faces (Jaworska et al. 2010) providing additional evidence for a more specific pharmacological action of psilocybin.

Mechanistically, we interpret the reduced neurophysiological response across all face valences as modulation of selective attention induced by psilocybin, consistent with previous studies, which demonstrated an attenuation of the visual attentional performance in a dose-dependent manner (Gouzoulis-Mayfrank et al. 2002; Carter et al. 2005; Vollenweider et al. 2007; Quednow et al. 2012).

Over both 168–189 and 211–242 ms poststimulus intervals we observed a pure change in response strength induced by psilocybin, consistent with a quantitative modulation of the attention level (Hillyard and Anllo-Vento 1998; Luck et al. 2000). Accordingly, Wronka and Walentowska's (2011) ERPs study demonstrated that when facial expressions were attended an increased N170 was measured for facial expressions vs. neutral faces. This was not the case when attention was directed to the face gender, suggesting a top-down attentional control on emotional face processing. In line with these results, Bressler et al. (2008) demonstrated a reduced attentional performance in visual tasks due to an increased top-down control. Furthermore, Bayle and Taylor (2010) suggested that attention modulates the structural encoding of faces, which occurs at ~170 ms

after the stimulus onset. The top-down control during emotional face processing was shown to modulate the activity within the amygdala, occipito-temporal visual cortex, orbitofrontal and posterior cingulate cortex, independent of the emotional valence (Pessoa et al. 2002; Bayle and Taylor 2010).

Evidence from animal and human PET imaging studies support the putative modulation of the top-down control induced by psilocybin. In fact, they suggest that activity within the PFC is modulated by the 5-HT_{2A} receptors on pyramidal cells (Wing et al. 1990; Vollenweider et al. 1997). Thus, stimulation of the 5-HT_{2A} receptors with psilocybin results in an enhanced top-down control of the PFC over limbic areas (Vollenweider et al. 1997; Vollenweider and Komater 2010 for discussion).

Additional evidence of a serotonin-induced modulation of the PFC top-down control over the limbic areas is provided by studies on patients with depression and anxiety, which are characterized by an impaired serotonergic system (Stuhrmann et al. 2011 for a review). Depressed patients were associated with a reduced PFC activity as well as hyperactivity within the amygdala, parahippocampal gyrus, and fusiform gyrus in response to negative stimuli. Likely, the hyperactivity is due to a reduced top-down control of the PFC (Johnstone et al. 2007; Bishop 2008).

Collectively, these results support the hypothesis of a modulation of the top-down control of the PFC over the limbic areas induced by the serotonergic system.

In conclusion, the present results are the first reporting the spatiotemporal brain dynamics of psilocybin-induced modulations of emotional face processing in healthy volunteers, providing new insights on the role of the serotonergic system on emotional face processing. We demonstrated a reduced neural response to both neutral and emotional faces induced by psilocybin, due to a psilocybin-induced increase in top-down control. The timing of our effects suggests that psilocybin modulates the fine-grained emotional face categorization.

Author Contributions

F.B. performed research, analyzed data, and wrote the paper. F.X.V. and E.S. designed, and wrote the paper. A.S. and M.K. designed and wrote the paper. T.P. performed research.

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Notes

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